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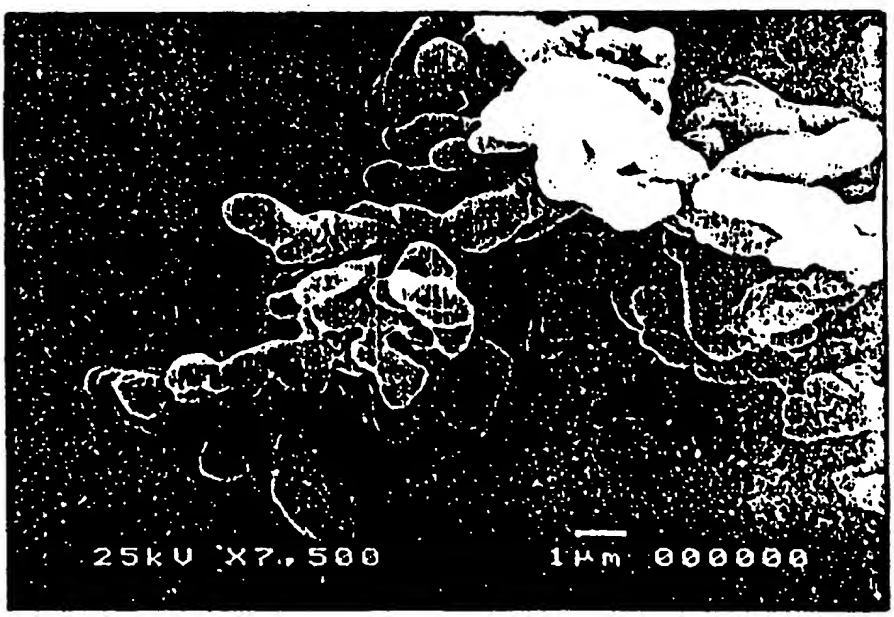
(54) Title: COMPOSITION COMPRISING FINELY DIVIDED, CRYSTALLINE PARTICLES OF BUDESONIDE

(57) Abstract

The invention provides finely divided, substantially crystalline particles of budesonide characterised in that they are substantially smooth and having a BET value from 1 to 4.5 m^2/g, process for their preparation, a pharmaceutical composition comprising said particles, the use of said particles in the treatment of and in the manufacture of a medicament for use in the treatment of a respiratory disorder, and a method of treatment of respiratory disorders by administration, to a host in need of such treatment, said particles.



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COMPOSITION COMPRISING FINELY DIVIDED, CRYSTALLINE PARTICLES OF BUDESONIDE

The invention provides finely divided particles of budesonide and a process for their preparation. The invention also relates to a pharmaceutical composition comprising said particles, the use of said particles in the treatment of and in the manufacture of a medicament for use in the treatment of a respiratory disorder, and a method of treatment of respiratory disorders by administration, to a host in need of such treatment, said particles.

Finely divided particles of budesonide are used in therapy in administration by inhalation where it is desired that the drug particles penetrate deep into the lung. Conventionally these finely divided drug particles are made by techniques such as micronization or grinding. A number of other techniques for their production are also available. Such techniques, and in particular micronization, can produce particles which have regions of partially amorphous structure and which have an irregular shape, but which are generally sufficiently stable for pharmaceutical use. However, these particles are liable to change their structure when kept in an adverse environment, such as is usual when a drug is stored (e.g. in high humidity which can cause agglomeration), and/or is in use by a patient. In the past the problem of the amorphous areas has been overcome by subjecting the particles to a conditioning process such as that disclosed in WO 95/05805 but the problem with the irregular shape of the particles remains. The shape of the particles is important because any irregularity increases the tendency of the particles to stick together. Thus they are harder to disperse in the lung. A solution to these problems has been sought.

According to the present invention the problem has been solved by providing finely divided, substantially crystalline particles of budesonide characterised in that they are substantially smooth and have a surface area BET gas absorption value of from 1, preferably from 2.0, to 4.5, preferably to 3.6 m^2/g.

The well-defined small particles of the present invention are a prerequisite for an efficient formulation for inhalation, which may be observed by e.g. an increased fraction of the dose

to the lung. Crystals with a low surface area have lower tendency to stick together than crystals with a higher surface area e.g irregular crystals.

The surface area was measured by BET gas absorption, e.g. as measured by a Flowsorb II 2300 or Gemini 2370, Micromeritics Co, USA, and described in ISO/TC24SC4N 55 (7th draft) and references therein.

The smoothness of the particles of the invention is illustrated by Figure 1 which is a Scanning Electron Micrograph (SEM) of the particles of the invention taken using a JEOL Scanning Microscope JSM-5200.

It is preferred that the finely divided particles according to the invention have a mass median diameter (MMD) of less than 10 μm, preferably less than 5 μm, more preferably less than 3 μm.

The particles according to the invention have a substantially crystalline form, preferably at least 95% by weight crystallinity wherein there are substantially no amorphous areas. The crystallinity of the particles of the invention is illustrated by the X-ray diffraction pattern of Figure 2. Preferably the particles of the invention have an energy of recrystallisation of less than 1.0 J/g, more preferably less than 0.5 J/g, as measured using a ThermoMetric 227 Thermal Activity monitor. The measurement was carried out by exposing samples of the particles to a temperature of 25°C and 94% relative humidity for 24 hours and recording the amount of heat given off by the sample.

The finely divided particles of the invention may be prepared by the co-introduction of a solution of budesonide in a solvent and of a supercritical fluid into an apparatus wherein the temperature and pressure of the apparatus are controlled such that dispersion and extraction of the solvent by the action of the supercritical fluid occur substantially simultaneously. Thus the active substance, budesonide, precipitates directly into the small respirable particles having the desired physio-chemical properties. A supercritical fluid is,

in general, a fluid at or above both its critical pressure and critical temperature; it is preferably carbon dioxide. The solvent used to dissolve budesonide is preferably an organic solvent, e.g. acetone or methanol. Preferably the process is carried out using the apparatus disclosed in WO 95/01221.

The finely divided particles according to the invention are preferably for use in the treatment of a respiratory disorder, e.g. asthma. The invention further provides a pharmaceutical composition comprising finely divided particles according to the invention in association with a pharmaceutically acceptable carrier or diluent, e.g. lactose. The invention also provides the use of the finely divided particles according to the invention in the manufacture of a medicament for use in the treatment of a respiratory disorder.

The finely divided particles according to the invention may be used in a variety of pharmaceutical formulations, e.g. in producing tablets, or for filling into capsules for oral use. Preferred, however, are finely divided particles to be used to produce inhalation formulations. Thus the finely divided particles according to the invention may be used on their own or in admixture with excipients, e.g. lactose, which are of a larger, or approximately of the same, particle size as the drug. Such powder formulations may be used in capsules, e.g. for use in the Spinhaler®, or in other inhalation devices, e.g. the Turbuhaler®, the Rotahaler®, the Diskhaler® or Diskus®. The finely divided particles according to the invention may also be treated further using known techniques, e.g. spheronization, to provide soft pellets, or soft granules, which are sufficiently strong to be filled into containers without disintegrating, but which are sufficiently weak to disintegrate into their fine constituent particles when administered by inhalation.

The invention is illustrated by the following Examples which should not be interpreted as limiting the invention.

Example 1

An acetone solution containing 1.0% w/v of budesonide was prepared and fed (0.3 ml/min) into the apparatus described in WO 95/01221 using a 0.15 μm nozzle. The flow rate of supercritical carbon dioxide was 10.0 ml/min. The working conditions were 100 bar and 60°C. A fine, smooth, white crystalline powder of budesonide having a BET value of 3.6m^2/g (measured using a Gemini 2375 V1.01) and a particle size of 2.25 μm (MMD) was obtained in 88% yield. The SEM of the powder is shown in Figure 1.

Example 2

An acetone solution containing 2.5% w/v of budesonide was prepared and fed (0.2 ml/min) into the same apparatus as used in Example 1. The flow rate of supercritical carbon dioxide was 9.0 ml/min. The working conditions were 100 bar and 80°C. A fine, smooth, white crystalline powder of budesonide was obtained which had the X-ray powder diffraction pattern shown in Figure 2.

Example 3

An acetone solution containing 1.0% w/v of budesonide was prepared and fed (1.5 ml/min) into the apparatus described in WO 95/01221 using a 0.35 μm nozzle. The flow rate of supercritical carbon dioxide was 45 ml/min. The working conditions were 100 bar and 60°C. A fine, smooth, white crystalline powder of budesonide having a BET value of 2.0m^2/g (measured using a Gemini 2375 V1.01) and a particle size of 4.62 μm (MMD) was obtained in 82% yield.

Example 4

An acetone solution containing 2.5% w/v of budesonide was prepared and fed (1.5 ml/min) into the apparatus described in WO 95/01221 using a 0.35 μm nozzle. The flow rate of supercritical carbon dioxide was 45 ml/min. The working conditions were 100 bar and 80°C. A fine, smooth, white crystalline powder of budesonide having a BET value of 2.5m^2/g (measured using a Gemini 2375 V1.01) and a particle size of 3.33 μm (MMD) was obtained in 83% yield.

Claims

1. Finely divided, substantially crystalline particles of budesonide characterised in that they are substantially smooth and having a BET value from 1 to 4.5 m^2/g.

2. Finely divided particles according to claim 1 characterised in that they have a BET value of from 2.0 to 3.6 m^2/g.

3. Finely divided particles according to claim 1 or 2 characterised in that they have an energy of recrystallisation of less than 1 J/g.

4. Finely divided particles according to claim 1, 2 or 3 characterised in that they have a mass median diameter of less than 10 μm.

5. Finely divided particles according to any one of the preceding claims for use in the treatment of a respiratory disorder.

6. A pharmaceutical composition comprising finely divided particles according to any one of the preceding claims in association with a pharmaceutically acceptable carrier or diluent.

7. Use of the finely divided particles according to any one of claims 1 to 5 in the manufacture of a medicament for use in the treatment of a respiratory disorder.

8. A method of treatment of a respiratory disorder comprising administration, to a host in need of such treatment, an effective dose of the finely divided particles according to any one of claims 1 to 4.

9. A process for preparation of finely divided particles according to any one of claims 1 to 5 characterised in co-introduction of a solution of budesonide in a solvent and of a

super-critical fluid into an apparatus, wherein the temperature and pressure are controlled such that dispersion and extraction of the solvent by the action of the supercritical fluid occur substantially simultaneously.

10. A process according to claim 9 wherein the supercritical fluid is carbon dioxide.

Fig 1

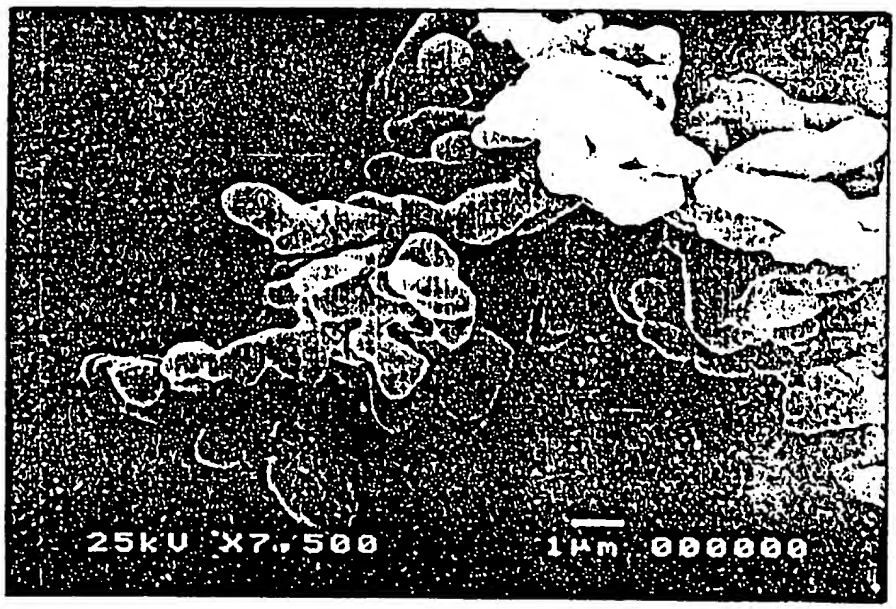
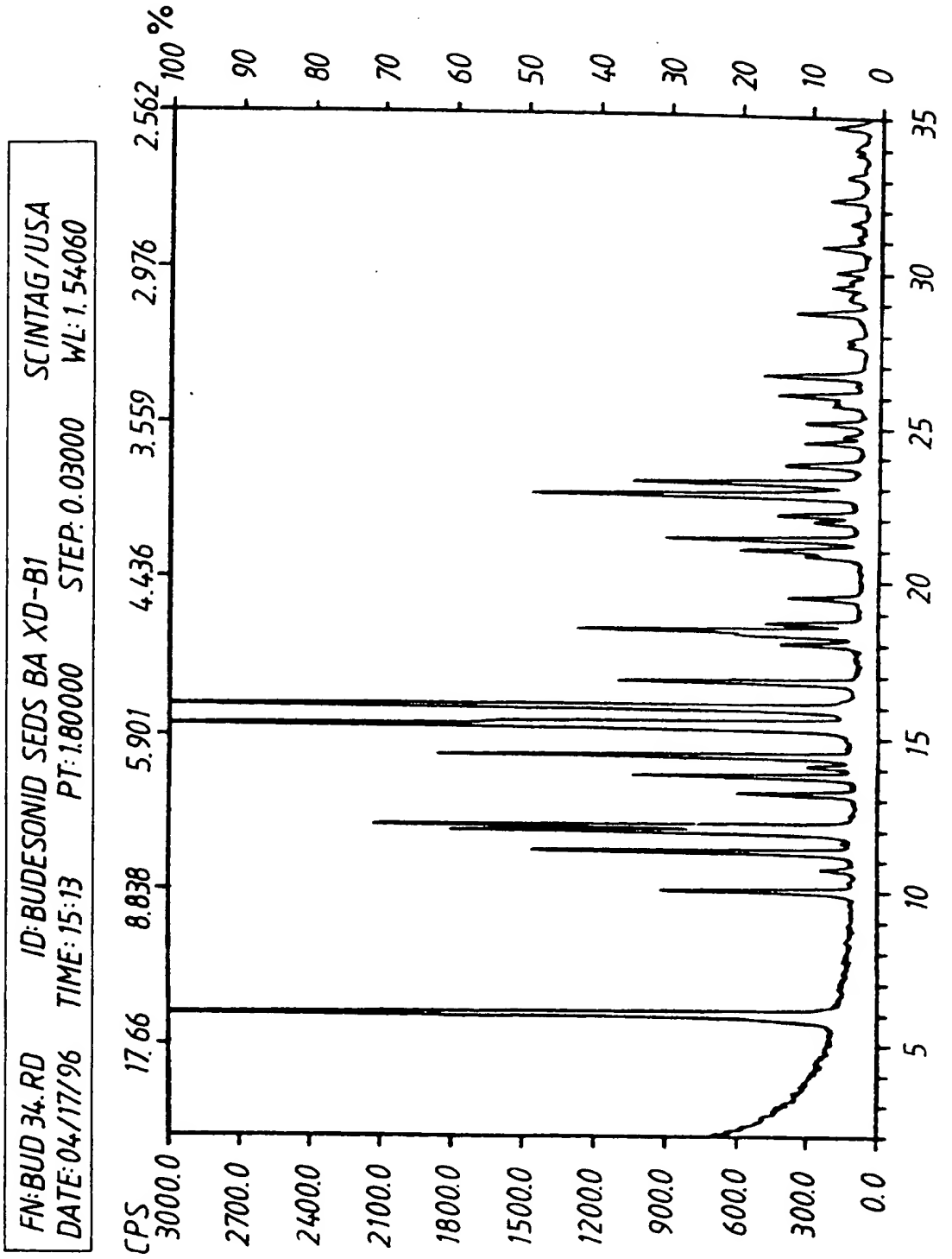


Fig. 2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00908

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/16, A61K 31/56
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, WPI, CAPLUS, SCISEARCH, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9505805 A1 (ASTRA AKTIEBOLAG), 2 March 1995 (02.03.95) --	1-10
X	WO 9501221 A1 (UNIVERSITY OF BRADFORD), 12 January 1995 (12.01.95) -- --------	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 Sept 1998	11 -09- 1998
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00908

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [x] Claims Nos.: 8
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Claim 8 is directed to method of treatment of the human or animal body by therapy methods practised on the human or animal body/ Rule 39.1(iv). Nevertheless, a search has been executed for this claims. The search has been based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.
PCT/SE 98/00908

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9505805 A1	02/03/95	AU 681186 B	21/08/97
		AU 7626494 A	21/03/95
		BR 9407320 A	16/04/96
		CN 1133004 A	09/10/96
		CZ 9600544 A	15/05/96
		EP 0717616 A	26/06/96
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		HU 9600447 D	00/00/00
		IL 110698 D	00/00/00
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		EP 0706421 A	17/04/96
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		NZ 267697 A	26/05/97

Fig.1

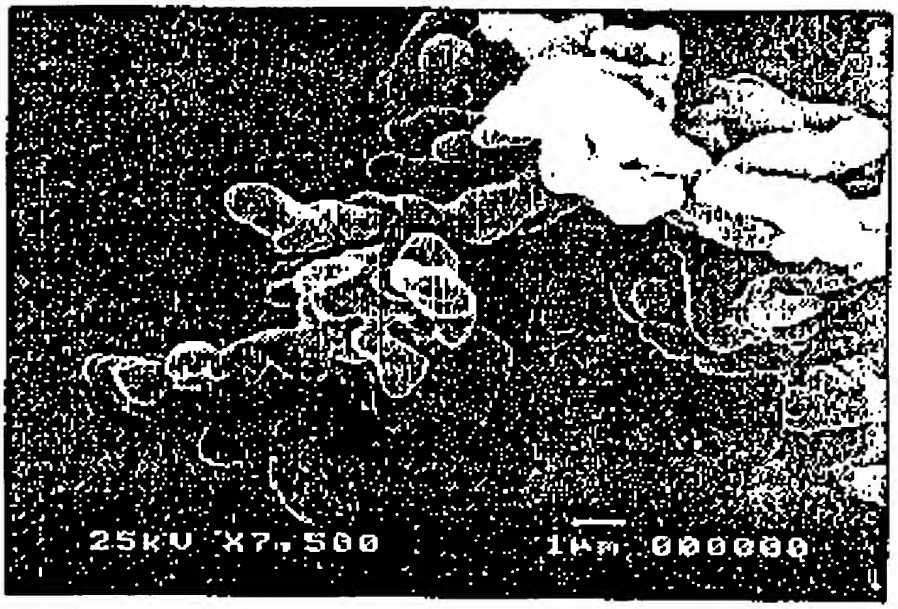

Fig 2